REMARKS

The Office Action mailed September 29, 2008, has been reviewed and considered. Claims 8, 10, 12, 14, 16 and 18-24 are currently pending in the application. Claims 8, 10, 12, 14, 16, and 18-24 stand rejected. Applicant has amended claims 23 and 24 (to correct grammatical errors) and added new claims 25-36. New claims 25-36 include limitations identified by the Office as satisfying the written description and enablement requirements of 35 U.S.C. § 112. Applicant, nevertheless, believes claims 8, 10, 12, 14, 16, and 18-24 are allowable despite the rejections, and respectfully requests reconsideration of the application as amended herein.

The Examiner has withdrawn the previous rejections under 35 U.S.C. § 103 and 112, first and second paragraphs.

The present application includes claims directed at methods of preparing 2-halo-2'-deoxyadenosine compounds. The methods permit a more efficient synthesis of desirable pharmaceutical agents useful in treating diseases. For example, practicing the claimed methods permits a more efficient synthesis of cladribine, an important agent for treating hairy-cell leukemia.

35 U.S.C. § 112 Claim Rejections

A. Claims 19-24

Claims 19-24 stand rejected under 35 U.S.C. § 112, first paragraph, as not satisfying the written description requirement. Applicants respectfully traverse this rejection, as hereinafter set forth.

Claims 19-24 contain one or more phrases to which the office objects, including the following:

(1) "a protecting group"

(2) "a 6-(substituted oxy) group having sufficient reactivity in an S_NAR replacement reaction"

(3) "substituted alkyl"

(4) "substituted aryl"

(5) "a halogen compound"

(6) "a 6-leaving group having lesser reactivity than that of the 2-amino group in a diazotization/chloro-dediazoniation displacement reaction"

Each phrase, however, satisfies 35 U.S.C. § 112, first paragraph, when read by one of ordinary skill in this art in light of the specification.

Section 112 requires an applicant's specification to contain a written description of the invention which reasonably conveys to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time of filing. According to the Manual of Patent Examining Procedure (MPEP), "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." §2163 (*citing Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d at 1384, USPQ at 94 (Fed. Cir. 1986). Furthermore, it is unnecessary that every nuance of the claims be explicitly described in the specification. *Id.* (*citing Vas-Cath* v. *Mahurkar*, 935 F.2d at 1563 (Fed. Cir. 2007). Thus, what is well-known or conventional to one of ordinary skill in a particular art need not be recited in exhausting detail to show possession of an invention.

Each the rejected phrases is addressed below.

1. <u>"A protecting group"</u>

The phrase "a protecting group" satisfies Section 112. The specification describes a number of specific protecting groups which may be used. As noted by the examiner, these include acyl and silyl. (Specification at ¶12.) An additional protecting group, benzoyl, was also described by the Applicant at ¶¶ 12,31. The specification also provides working examples using various protecting groups. (*See e.g.* examples 1 and 2 identifying acetyl and benzoyl protecting groups & Fig. 1.) Moreover, the specification teaches that protecting groups, well-known in this art may be employed. (*Id.* at ¶¶ 12, 73-78.) Thus, Applicant's specification described a number of suitable, protecting groups demonstrating possession of the invention.

For at least these reasons, claims involving the phrase "a protecting group" satisfy Section 112.

2. "A 6-(substituted oxy) group having sufficient reactivity in an S_NAR replacement reaction"

The phrase "a 6-(substituted oxy) group having sufficient reactivity in an S_NAR replacement reaction" satisfies Section 112. The term S_NAR is a widely known abbreviation referring to nucleophilic aromatic substitution. This type of reaction mechanism is well known to one of ordinary skill in this art. In such reactions, a nucleophile (a reagent which forms a new chemical bond by donating electrons) displaces a leaving group which breaks a chemical bond. Thus, one of ordinary skill in this art would understand that the "6-(substituted oxy) group" is the leaving group displaced by a nucleophile, and the nucleophile becomes the new substituent at the C-6 position of the purine ring in the recited nucleoside structure.

The specification describes a number of suitable groups which may be used. As noted by the examiner, these include alkylsulfonyl, arylsulfonyl, and chloride. (Specification at ¶14.) The specification also provides working examples using various groups such as 6-O-Ts (tosylate) and 6-O-TiPBS (triisopropylbenzene-sulfonyl). (*See e.g.* ¶16.) Thus, Applicant's specification described a number of suitable groups demonstrating possession of the invention.

For at least these reasons, claims involving the phrase "a 6-(substituted oxy) group having sufficient reactivity in an S_NAR replacement reaction" satisfy Section 112.

3. "Substituted alkyl"

The phrase "substituted alkyl" satisfies Section 112. Its use in the claims occurs when identifying a "6-(substituted oxy) group" and reagents added to obtain the "6-substituted oxy) group." As explained above, the "6-(substituted oxy) group" becomes a leaving group during a nucleophilic aromatic substitution reaction. The specification describes several suitable groups and reagents for obtaining those leaving groups. Among them are alkyl- and substituted alkyl-sulfonyl groups which the specification identifies as "sulfonyl compounds having the formula $R'SO_2$-X." (Specification at ¶15.) Moreover, the specification also states that R' is alkyl, substituted alkyl, cycloalkyl, aryl, or substituted aryl. (*Id.* emphasis added.) Thus, the specification discloses a number of suitable sulfonyl compounds.

Alkyl sulfonyl groups are commonly used functional groups that, when bound to an oxygen (such as the C-6 oxygen in the claimed structures), form leaving groups for nucleophilic substitution reactions. For example, methylsulfonyl groups form mesylates, $CH_3SO_3^-$. Similarly, substituted alkyl sulfonyl groups form leaving groups for nucleophilic substitution reactions. For example, trifluoromethylsulfonyl groups form triflates, $CF_3SO_3^-$.

While triflates and mesylates are the more commonly used alkyl sulfonyl and substituted alkyl sulfonyl groups, one of ordinary skill in this art understands that other similar groups can be used. As noted by the examiner, substituted alkyl includes fluoroalkyl, which would encompass triflates. Fluoroalkyl was specifically mentioned in the specification at ¶15. Fluoroalkyl was not identified in a limiting sense but as exemplary: "including but not limited to fluroalkyl." (*Id.*)

For at least these reasons, claims involving the phrase "substituted alkyl" satisfy Section 112.

4. "Substituted aryl"

Similarly, the phrase "substituted aryl" satisfies Section 112. Its use in the claims also occurs when identifying a "6-(substituted oxy) group" and reagents added to obtain the "6-substituted oxy) group." The specification describes several sulfonyl groups including aryl and substituted aryl sulfonyl. (¶15.)

Arylsulfonyl groups, like alkylsulfonyl groups, are commonly used functional groups that, when bound to an oxygen (such as the C-6 oxygen in the claimed structures), form leaving groups for nucleophilic substitution reactions. For example, benzene sulfonyl groups form besylates, $C_6H_5SO_3^-$. Similarly, substituted aryl sulfonyl groups form leaving groups for nucleophilic substitution reactions. For example p-toluene sulfonyl groups form tosylates, $CH_3C_6H_4SO_3^-$ (a tosyl group, abbreviated Ts or Tos is $CH_3C_6H_4SO_2$). Tosylates were specifically identified by the Applicant's specification at ¶15. Also 2,4,6-triisopropylbenzenesulfonyl, known as a TiPBS group, is commonly used and disclosed in the specification. (*Id.* at ¶¶15-16.)

While besylate and tosylate groups may be more commonly used aryl and substituted sulfonyl groups, one of ordinary skill in this art understands that others can

be used – such as the TiPBS group mentioned in the specification. For at least these reasons, claims involving the phrase "substituted aryl" satisfy Section 112.

5. "A halogen compound"

The phrase "a halogen compound" satisfies Section 112. The specification describes a number of specific halogen compounds which may be used. As noted by the examiner, these include metal chlorides, metal chloride salts, acyl chlorides, sulfonyl chlorides, silyl chlorides, alkyl and aryl substituted ammonium chlorides. (Specification at ¶20.) An additional halogen compound was also described by the Applicant at ¶ 17, namely phosphoryl chloride. The specification also provides working examples using various halogen compounds. (*See e.g.* Fig. 1 step d, ¶¶21-24.) Thus, Applicant's specification described a number of suitable groups demonstrating possession of the invention.

For at least these reasons, claims involving the phrase "a halogen compound" satisfy Section 112.

6. "A 6-leaving group having lesser reactivity than that of the 2-amino group in a diazotization/chloro-dediazoniation displacement reaction"

The phrase "a 6-leaving group having lesser reactivity than that of the 2-amino group in a diazotization/chloro-dediazoniation displacement reaction" satisfies Section 112. This phrase identifies a functional group at the C-6 position of the nucleoside present prior to a diazotiazation/chlro-dediazoniation reaction.

The specification describes a number of suitable groups which may be used. As noted by the examiner, these include alkylsulfonyl, arylsulfonyl, and chloride. (Specification at ¶14.) As described above, the specification also describes substituted alkyl, cycloalkyl, and substituted arylsulfonyl groups. (*Id.* at ¶15.) Moreover, the specification provided working examples. (*See e.g.* ¶¶17-23, Fig. 2.) Thus, Applicant's specification described a number of suitable, leaving groups demonstrating possession of the invention.

For at least these reasons, claims involving the phrase "a 6-(substituted oxy) group having sufficient reactivity in an S_NAR replacement reaction" satisfy Section 112.

7. Functional Language Is Also Appropriate

The Office also states that "a 6-(substituted oxy) group having sufficient reactivity in an S_NAR replacement reaction" and "a 6-leaving group having lesser reactivity than that of the 2-amino group in a diazotization/chloro-dediazoniation displacement reaction" are functional limitations. The Office relies on court decisions including *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 2007), and others for the proposition that functional language cannot be used to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. The Office errs and the decisions cited are distinguishable.

The MPEP at Section 2163 is instructive:

> The claimed invention *as a whole* may not be adequately described where an invention is described *solely* in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between structure of the invention and its function.

(2100-166.) Applied here, the claimed invention is not defined *solely* by the two phrases with which the Office has taken issue. Each claim includes a chemical formula for nucleosides which conveys specific structural information.

The Applicant's use of functional language in the two phrases describes the chemical properties of substituents at two particular locations in the structurally defined nucleosides, namely the 2 and 6 positions of the purine. Those chemical properties relate to the reactivity of the nucleoside when performing another step in the claimed method. These particular functional phrases used in the claims are clearly understood by those of ordinary skill in the art, and the Office Action does not provide evidence or reasoning to the contrary.

Moreover, the cases cited by the Office fail to support the Office's position. In *University of California*, claims to vertebrate insulin cDNA were invalidated. The court reasoned that claims to chemical materials with formulas normally have adequate description while a claim to genetic material with a generic statement such as vertebrate insulin cDNA without more is not.

Here, Applicant's claims in fact use chemical formulas to define the claimed methods for preparing 2-halo-2'-deoxyadenosine compounds. It is unnecessary that a

chemical substituent in a well-defined formula also be defined with structure, when such substituents are described with sufficient detail that one skilled in the art can reasonable conclude that the inventor has possession of the claimed invention. This is particularly true when the specification includes several working examples.

8. Summary

The Applicant's specification, when read by one of ordinary skill satisfies 35 U.S.C. § 112, first paragraph. It is unnecessary for an Applicant to disclose in detail what is conventional or well known in the art, and the specification provides structural information and working examples for each of the disputed phrases. Applicant, therefore, respectfully requests withdrawal of this rejection.

B. Claims 8, 10, 12, 14, 16, and 18

Claims 8, 10, 12, 14, 16, and 18 stand rejected under 35 U.S.C. § 112, second paragraph, on grounds of lack of enablement. Specifically, the Office Action asserts that the specification, while being enabling for some temperatures less than 0°C at paragraph 37 of the specification, does not reasonably provide enablement for all temperatures less than 0°C. Applicants respectfully traverse this rejection for the following reasons.

The Office Action in analyzing the *Wands* factors, specifically the state of the prior art, states that "It is well known in the art that no chemical reactions occur at absolute zero."

Again, the MPEP is instructive. "A patent need not teach, and preferably omits, what is well known in the art." §2164.01(a) (*citing In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Applicant's patent need not teach that the claimed methods cannot operate at absolute zero. One of ordinary skill in this art would not undertake experimentation to reach this conclusion.

While the Office acknowledges that Applicant provided working examples in the specification (¶16, and see Examples), it argues that guidance is not given for a lower limit for the recited temperature range. Applicant believes such guidance is unnecessary.

One of ordinary skill in this art understands that the kinetic activity of a reaction decreases with reduced temperature. Moreover, the rate at which a reaction achieves

equilibrium is also affected by temperature. Such basic notions of chemistry are known to the artisan whether the relative skill in this art is high or low. For example, the Arrhenius equation is a familiar rule in chemistry. This rule states that the rate of a chemical reaction doubles for each increase in temperature of ten degrees. Therefore, one of ordinary skill in this art would not have to undertake undue experimentation to practice the claimed invention, namely "at or less than a temperature of 0° C"

MPEP Section 2164.08(b) also seems to contradict the Office's position:

> The presence of inoperative embodiments with the scope of a claim does not necessarily render a claim nonenabled . . . A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enable scope because undue experimentation was not involved in determining those embodiment that were operable. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 219 (CCPA 1976).

Here, the Office has identified a single inoperative embodiment, namely carrying out one step of the claimed methods at absolute zero. One of ordinary skill in this art, however, would not have to perform undue experimentation to determine this.

For at least these reasons, Applicant's specification satisfies 35 U.S.C. § 112, second paragraph. The Applicant's claimed methods can be practiced without undue experimentation. Applicant, therefore, respectfully requests withdrawal of this rejection.

SUMMARY

Pending claims 8, 10, 12, 14, 16 and 18-24 satisfy the requirements under 35 U.S.C. § 112. Applicants respectfully request the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorneys for the Applicants via telephone if such communication would expedite this application.

Respectfully submitted,

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